Clinical Prediction Rule for Identifying Children With Cerebrospinal Fluid Pleocytosis at Very Low Risk of Bacterial Meningitis

Lise E. Nigrovic; Nathan Kuppermann; Charles G. Macias; et al.

http://jama.ama-assn.org/cgi/content/full/297/1/52

Correction
Contact me if this article is corrected.

Citations
This article has been cited 32 times.
Contact me when this article is cited.

Topic collections
Bacterial Infections; Neurology; Meningitis; Pediatrics; Pediatrics, Other; Prognosis/Outcomes; Infectious Diseases
Contact me when new articles are published in these topic areas.

Related Articles published in the same issue
Meningitis

Related Letters
Prediction Rule for Bacterial Meningitis in Children

In Reply:
Clinical Prediction Rule for Identifying Children With Cerebrospinal Fluid Pleocytosis at Very Low Risk of Bacterial Meningitis

Lise E. Nigrovic, MD, MPH
Nathan Kuppermann, MD, MPH
Charles G. Macias, MD, MPH
Christopher R. Cannavino, MD
Donna M. Moro-Sutherland, MD
Robert D. Schremmer, MD
Sandra H. Schwab, MD
Dewesh Agrawal, MD
Karim M. Mansour, MD
Jonathan E. Bennett, MD
Yiannis L. Katsogridakis, MD, MPH
Michael M. Mohseni, MD
Blake Bulloch, MD
Dale W. Steele, MD
Ron L. Kaplan, MD
Martin I. Herman, MD
Subhankar Bandyopadhyay, MD
Peter Dayan, MD, MSc
Uyen T. Truong, MD
Vincent J. Wang, MD
Bema K. Bonsu, MD
Jennifer L. Chapman, MD
Richard Malley, MD

for the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics

A LTHOUGH BACTERIAL MENINGITIS is the greatest concern when evaluating and treating children with cerebrospinal fluid (CSF) pleocytosis,1 the majority of these children have aseptic rather than bacterial meningitis.2,3 However, because exclusion of bacterial meningitis requires negative CSF (and blood) cultures after 2 to 3 days of incubation,4,5 most children with CSF pleocytosis are admitted to the hospital to receive broad-spectrum antibiotics while awaiting culture test results. With the widespread introduction of highly effective bacterial conjugate vaccines against Haemophilus influenzae type b6,7 and Streptococcus pneumoniae,8-12 there has been a significant decrease in the incidence of bacterial meningitis in US children. This has further reduced the probability that a child with CSF pleocytosis will have bacterial meningitis. A

See also Patient Page.
highly accurate decision support tool that could identify which children with CSF pleocytosis had a near-zero risk of bacterial meningitis by using clinical and laboratory parameters readily available at the time of clinical presentation could guide decision making and limit unnecessary hospital admissions and prolonged antibiotic use.

We previously developed a clinical prediction rule, the Bacterial Meningitis Score,1 which classifies patients at very low risk of bacterial meningitis if they lack all of the following criteria: positive CSF Gram stain, CSF absolute neutrophil count (ANC) of at least 1000 cells/µL, CSF protein of at least 80 mg/dL, peripheral blood ANC of at least 10 000 cells/µL, and a history of seizure before or at the time of presentation (Box). In the original study of 696 children hospitalized with CSF pleocytosis at a single institution, we derived the Bacterial Meningitis Score on a random two thirds of the children in the data set, and validated the score on the remaining one third of the children.3,13 We found that of the 144 patients classified as very low risk in the validation set none had bacterial meningitis (negative predictive value, 100%; 95% confidence interval [CI], 97%-100%). In the validation set, the sensitivity of the Bacterial Meningitis Score for bacterial meningitis (ie, having ≥1 prediction rule risk factor) was 100% (37/37, 95% CI, 91%-100%).

For several reasons, clinical prediction rules are often less accurate when tested in a new clinical setting.14 First, the assessment of either the predictor or outcome variables may not be reproducible with new patients and physicians.15 Second, as in the case of bacterial meningitis since the advent of conjugate polysaccharide vaccines, the epidemiology of the disease or associated diagnostic testing studied may change over time and thus potentially affect the performance of any prediction rule. Finally, the observed relationships between predictors and outcome may depend on unique characteristics of the derivation population and may differ if tested in a new patient population (model overfitting to the original data set).16 Therefore, before implementation of a clinical prediction rule, the model should be validated externally using a different patient population and clinical setting from those on which the prediction rule was developed.13,15-19 In practice, these methodological standards are seldom met.18

We desired to validate the Bacterial Meningitis Score in the era of widespread conjugate pneumococcal vaccination on a large population of children evaluated in emergency departments across the United States. To this end, we performed a validation study by using a network of 20 academic medical centers, as part of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. We planned to review the records of all children with meningitis evaluated in the emergency departments of these centers over a 4-year period. Thus, our study goal was to externally validate the Bacterial Meningitis Score, focusing primarily on the ability of the rule to identify patients at very low risk of bacterial meningitis. We also determined whether further refinement of the Bacterial Meningitis Score would simplify and improve the performance of this clinical prediction rule.

**METHODS**

**Multicenter Collaborative Research Network**

The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics reviewed, critiqued, and approved the study protocol. We identified coinvestigators from 20 emergency departments located across the United States, which routinely participate in this research network. Collectively, more than 1 million children per year are evaluated in emergency departments in these centers. Participating institutions were located in 16 different states, plus the District of Columbia, and included free-standing pediatric centers (n = 17) and general emergency departments (n = 3).

Approval for the study and for data sharing with the coordinating institution was granted by the institutional review boards at each participating institution. Requirement for informed consent was waived by the institutional review boards of each participating institution.

**Patient Identification**

We reviewed the medical records of all patients aged 29 days to 19 years who received a diagnosis of meningitis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], with the following codes: bacterial meningitis, 320.0-320.9; viral meningitis, 046.0-048.9; or unspecified meningitis, 321.0-322.9) at each of the participating emergency departments between January 1, 2001, and June 30, 2004. For consistency, only patients who had lumbar punctures performed in the emergency department of the study institutions were included (n = 4369). We ensured complete capture of children with bacterial meningitis by cross-checking each institution’s microbiology logs and by including all patients with CSF cultures growing bacterial pathogens (5 patients with bacterial meningitis were not identified by ICD-9 codes). Cultures...
that grew *Staphylococcus epidermidis*, *Streptococcus viridans*, or *Propionibacterium acnes* were considered to be classified as being negative.

**Inclusion Criteria**

Children were classified as having meningitis and included in the study if either of the following criteria applied: CSF pleocytosis (CSF white blood cells \(\geq 10\) cells/\(\mu L\), corrected for the presence of CSF red blood cells using a 1:500 ratio of leukocytes to erythrocytes usually found in peripheral blood\(^{20,21}\)) or a positive CSF culture for a bacterial pathogen.

**Exclusion Criteria**

We excluded patients with CSF pleocytosis who would require hospital admission regardless of the risk of bacterial meningitis, including children with any of the following conditions or clinical findings: critical illness (defined as severely altered mental status, evidence of cerebral herniation, need for respiratory or blood pressure support), purpura, presence of ventricular shunt device, recent neurosurgery, immunosuppression, other bacterial infections necessitating inpatient antibiotic therapy (eg, urinary tract infections in infants <3 months, periorbital cellulitis, deep abscess, bone or joint infections, or known bacteremia), or active Lyme disease. Because antibiotic pretreatment can alter CSF profiles\(^{22,23}\) and result in falsely negative blood cultures, CSF cultures, or both, we excluded patients who had received oral or parenteral antibiotics within 72 hours before their lumbar puncture.

**Case Definitions**

We defined a child as having bacterial meningitis if there was a positive CSF culture, CSF pleocytosis in association with a positive blood culture for a bacterial pathogen, or CSF pleocytosis in association with a positive CSF latex agglutination test for a bacterial pathogen. We defined a child as having aseptic meningitis if there was CSF pleocytosis with negative bacterial cultures of blood and CSF and a negative CSF latex agglutination test (if obtained).

Patients who did not have a CSF culture obtained were excluded (\(n=15\)); however, we did include patients who did not have blood cultures obtained provided that a CSF culture was obtained (\(n=342\)). Three of these patients had bacterial meningitis based on a positive CSF culture. The remaining 339 patients, all of whom had negative CSF cultures, had either Lyme meningitis (7 [2% of patients with aseptic meningitis and no blood culture]), enteroviral meningitis (79 [23%]), or unspecified aseptic meningitis (253 [75%]). Except for the patients with Lyme meningitis (who each received parenteral antibiotics for 21 days), none of these patients received a course of antibiotics for bacterial meningitis (defined by a course of antibiotics \(\geq 7\) days).

**Data Collection**

Each of the coinvestigators reviewed the computerized medical records, written medical records, or both for all study patients at their site. Patient information was entered by each investigator either onto a structured case report form (7 centers) or directly into a computerized database (identical in structure to the case report form) by using Microsoft Access database software\(^{24}\) (13 centers).

Because we were also interested in refining the Bacterial Meningitis Score prediction rule in addition to validating the Bacterial Meningitis Score, we collected and recorded the following information: patient demographics (date of birth, date of presentation, sex), clinical data (coexisting medical conditions, antibiotic pretreatment, vaccination status, triage temperature and duration of fever at the time of presentation, occurrence and timing of seizures), physical examination findings (presence of rash, meningeal signs, and papilledema), laboratory test results (peripheral complete blood cell count and differential, peripheral glucose, CSF white blood cell count and differential, CSF red blood cell count, CSF glucose, CSF protein, CSF Gram stain, blood and CSF cultures), and other microbiology testing that was performed (herpes simplex virus, enteroviral or Lyme CSF polymerase chain reaction latex agglutination testing, *Borrelia burgdorferi* serology, and viral and/or mycobacterial culture). We also determined clinical outcome, final clinical diagnosis, length of hospital stay, and duration of parenteral antibiotics by medical record review. In case of discrepancies between clinicians in the medical record, only the attending physician’s documentation was considered. When more than 1 CSF cell count was performed, the tube with the fewest red blood cells was always used regardless of its order in the sequence of collection.

**Bacterial Meningitis Score Validation**

In the main analysis, we evaluated the performance of the Bacterial Meningitis Score for predicting patients at very low risk of bacterial meningitis. Patients presenting with any predictors in the Bacterial Meningitis Score prediction rule were considered not to be at very low risk of bacterial meningitis. Patients missing data for any of the predictors were excluded from this analysis unless they had 1 or more positive predictors among those that could be evaluated, in which case they were considered not to be at very low risk for bacterial meningitis. We evaluated the performance of the rule with respect to sensitivity, specificity, negative predictive value, and positive and negative likelihood ratios for bacterial meningitis, and calculated 95% CIs where appropriate.

**Bacterial Meningitis Score Refinement**

To attempt to refine the Bacterial Meningitis Score, we performed in a subsequent analysis binary recursive partitioning using a classification tree algorithm. To approximate clinical decision making, we assigned in the analysis a relative cost of 100 for misclassifying a patient with bacterial meningitis as having aseptic meningitis. The recursive partitioning algorithm gener-
VALIDATION OF A CLINICAL PREDICTION RULE FOR BACTERIAL MENINGITIS

RESULTS
Patients
We identified 4369 children who met the inclusion criteria (Figure). We excluded 515 patients who would have required admission regardless of their risk of bacterial meningitis, 544 patients who had received antibiotic treatment before their lumbar puncture, and 15 patients who had no CSF culture obtained. Patients could be excluded for more than 1 reason. Among 3295 remaining patients with CSF pleocytosis, 121 (3.7%; 95% CI, 3.1%-4.4%) had bacterial meningitis and 3174 (96.3%; 95% CI, 95.5%-96.9%) had aseptic meningitis.

Characteristics of patients with bacterial and aseptic meningitis are shown in Table 1. All patients (n=121) with bacterial meningitis and 2518 patients (80%) with aseptic meningitis were admitted to the hospital. The median length of parenteral antibiotic therapy was 14 days (interquartile range, 10-14 days) for patients with bacterial meningitis and 2 days (interquartile range, 1-2 days) for patients with aseptic meningitis. No deaths occurred among the patients with bacterial meningitis who met the study inclusion criteria (and thus did not present critically ill). Only 1 patient, a 17-year-old with aseptic meningoencephalitis, died.

Figure. Patient Flow Diagram, Including the Classification Performance of the Bacterial Meningitis Score

©2007 American Medical Association. All rights reserved.
The etiology of bacterial meningitis was as follows: *S. pneumoniae* (35 patients [29%]), *Neisseria meningitidis* (33 [27%]), group B Streptococcus (24 [20%]), *Escherichia coli* (9 [7%]), *H influenzae* (7 [6%, all nontypable]), other gram-negative rods (7 [6%]), *Listeria monocytogenes* (3 [2.5%]), and group A Streptococcus (3 [2.5%]). The bacterial pathogen was identified by both CSF and blood culture in 65 patients (54%), CSF culture alone in 47 (39%), and blood culture alone in 9 (7%). No patient had a positive CSF latex agglutination test without either a positive CSF or blood culture.

Of the patients with aseptic meningitis, 1128 (36%) had enteroviral polymerase chain reaction testing performed, 391 (12%) herpes simplex virus polymerase chain reaction, 615 (19%) viral culture, and 231 (7%) *B burgdorferi* serology. Fifty-two percent of tested patients had a specific pathogen identified (enterovirus: n=839 [74% of all patients tested]; herpes simplex virus: n=6 [2%]; and *B burgdorferi*: n=24 [10%]).

### Performance of the Bacterial Meningitis Score

The Bacterial Meningitis Score was calculated for 2903 (88%) of 3295 study patients and could not be calculated for 392 patients (12%) due to missing predictor data (none of the 392 had bacterial meningitis). Among the 2903 patients, the frequency of bacterial meningitis increased with greater numbers of additional Bacterial Meningitis Score risk factors. The Bacterial Meningitis Score was calculated for 392 patients (12%) due to missing predictor data (none of the 392 had bacterial meningitis). Among the 2903 patients, the frequency of bacterial meningitis increased with greater numbers of additional Bacterial Meningitis Score risk factors.

#### Table 1. Characteristics of the 3295 Study Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Bacterial Meningitis (n = 121)</th>
<th>Aseptic Meningitis (n = 3174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>0.4 (0.2-2.6)</td>
<td>4.6 (0.2-9.8)</td>
</tr>
<tr>
<td>Male sex</td>
<td>83 (69)</td>
<td>1836 (58)</td>
</tr>
<tr>
<td>Presentation during enteroviral season†</td>
<td>34 (28)</td>
<td>2174 (69)</td>
</tr>
<tr>
<td>History of seizure before or at the time of presentation</td>
<td>7 (6)</td>
<td>80 (3)</td>
</tr>
<tr>
<td>Peripheral blood, median (IQR), cells/µL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count</td>
<td>14,400 (8600-22,000)</td>
<td>10,700 (8300-13,900)</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>10,176 (3759-17,315)</td>
<td>5890 (3604-8786)</td>
</tr>
<tr>
<td>Cerebrospinal fluid, median (IQR), cells/µL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count</td>
<td>1240 (274-3435)</td>
<td>120 (40-300)</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>952 (155-2784)</td>
<td>29 (7-112)</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>30 (12-53)</td>
<td>56 (49-64)</td>
</tr>
<tr>
<td>Protein, mg/dL</td>
<td>171 (85-251)</td>
<td>47 (32-69)</td>
</tr>
<tr>
<td>Positive CSF Gram stain</td>
<td>74 (61)</td>
<td>6 (0.2)</td>
</tr>
<tr>
<td>Admitted to the hospital</td>
<td>121 (100)</td>
<td>2518 (80)</td>
</tr>
<tr>
<td>Duration of parenteral antibiotics, median (IQR), d</td>
<td>14 (10-14)</td>
<td>2 (1-2)</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

SI conversion: To convert glucose to mmol/L, multiply by 0.0555.

#### Table 2. Risk of Bacterial Meningitis for Patients With 1, 2, or 3 or More Bacterial Meningitis Score Predictors

<table>
<thead>
<tr>
<th>Bacterial Meningitis Score Predictors Present</th>
<th>No. of Children With CSF Pleocytosis</th>
<th>No (% of Children With Bacterial Meningitis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Predictor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive CSF Gram stain</td>
<td>12</td>
<td>7 (58)</td>
</tr>
<tr>
<td>CSF ANC ≥1000 cells/µL</td>
<td>11</td>
<td>1 (9)</td>
</tr>
<tr>
<td>CSF protein ≥80 mg/dL</td>
<td>445</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Peripheral blood ANC ≥10,000 cells/µL</td>
<td>413</td>
<td>7 (2)</td>
</tr>
<tr>
<td>History of seizure before or at the time of presentation</td>
<td>43</td>
<td>1 (2)</td>
</tr>
<tr>
<td>2 Predictors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive CSF Gram stain and CSF ANC ≥1000 cells/µL</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Positive CSF Gram stain and CSF protein ≥80 mg/dL</td>
<td>14</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Positive CSF Gram stain and peripheral blood ANC ≥10,000 cells/µL</td>
<td>5</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Positive CSF Gram stain and seizure</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>CSF ANC ≥1000 cells/µL and CSF protein ≥80 mg/dL</td>
<td>30</td>
<td>10 (33)</td>
</tr>
<tr>
<td>CSF ANC ≥1000 cells/µL and peripheral blood ANC ≥10,000 cells/µL</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>CSF ANC ≥1000 cells/µL and seizure</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>CSF protein ≥80 mg/dL and peripheral blood ANC ≥10,000 cells/µL</td>
<td>46</td>
<td>7 (15)</td>
</tr>
<tr>
<td>CSF protein ≥80 mg/dL and seizure</td>
<td>12</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Peripheral blood ANC ≥10,000 cells/µL and seizure</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>≥3 Predictors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All combinations</td>
<td>76</td>
<td>58 (76)</td>
</tr>
<tr>
<td>Total patients with ≥1 predictor</td>
<td>1133</td>
<td>119 (10.5)</td>
</tr>
</tbody>
</table>

Abbreviations: ANC, absolute neutrophil count; CSF, cerebrospinal fluid; NA, not applicable.
low risk by the Bacterial Meningitis Score, 119 (10%) had bacterial meningitis and 1070 (90%) had aseptic meningitis. The sensitivity of the Bacterial Meningitis Score (ie, having ≥1 Bacterial Meningitis Score risk factor) for bacterial meningitis was 98.3% (119/121 patients with a Bacterial Meningitis Score calculated; 95% CI, 94.2%-99.8%) and the specificity was 61.5% (1712/2782; 95% CI, 59.7%-63.3%). The positive and negative likelihood ratios were 2.56 (95% CI, 2.43-2.69) and 0.03 (95% CI, 0.01-0.11), respectively.

Misclassified Patients

The Bacterial Meningitis Score misclassified 2 patients with bacterial meningitis as having aseptic meningitis. Both of these patients were infants between 1 and 2 months old with *E coli* meningitis and urinary tract infections, but with negative urinalyses at presentation (TABLE 4).

**Bacterial Meningitis Score Refinement**

We attempted to refine the prediction model using recursive partitioning analysis. The resulting decision tree identified the following predictors of bacterial meningitis in order of importance: CSF protein level of 80 mg/dL or higher, positive CSF Gram stain, and peripheral ANC of 10 000 cells/µL or more. Of 1786 patients with none of the 3 variables in the recursive partitioning model, 3 (0.2%) had bacterial meningitis (negative predictive value, 99.8%; 95% CI, 99.5%-100%). The recursive partitioning model misclassified the same 2 infants with *E coli* meningitis as having aseptic meningitis missed by the Bacterial Meningitis Score risk factor) for bacterial meningitis. Both of these patients were infants between 1 and 2 months old with *E coli* meningitis and urinary tract infections, but with negative urinalyses at presentation (TABLE 4).

**Table 3. Bivariate and Multivariate Adjusted Odds Ratios of Bacterial Meningitis for Each of the Bacterial Meningitis Score Predictors**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive cerebrospinal fluid Gram stain</td>
<td>866.1 (384.4-2093.2)</td>
<td>653.7 (216.6-1727.8)</td>
</tr>
<tr>
<td>Cerebrospinal fluid ANC ≥1000 cells/µL</td>
<td>47.2 (30.3-73.6)</td>
<td>8.0 (3.8-17.0)</td>
</tr>
<tr>
<td>Cerebrospinal fluid protein ≥80 mg/dL</td>
<td>17.9 (11.3-28.3)</td>
<td>12.2 (5.7-26.0)</td>
</tr>
<tr>
<td>Peripheral blood ANC ≥10 000 cells/µL</td>
<td>4.8 (3.3-6.9)</td>
<td>4.1 (2.2-8.0)</td>
</tr>
<tr>
<td>History of seizure before or at the time of presentation</td>
<td>2.4 (1.1-6.3)</td>
<td>3.7 (1.0-13.4)</td>
</tr>
</tbody>
</table>

*Abbreviations: ANC, absolute neutrophil count; CI, confidence interval. *Adjusted for the other Bacterial Meningitis Score predictors.

**Table 4. Characteristics of the 2 Patients With Bacterial Meningitis Misclassified by the Bacterial Meningitis Score**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age, mo</td>
<td>1.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Peripheral blood, cells/µL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count</td>
<td>12 300</td>
<td>12 300</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>8100</td>
<td>6600</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count, cells/µL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count, cells/µL</td>
<td>23</td>
<td>540</td>
</tr>
<tr>
<td>Absolute neutrophil count, cells/µL</td>
<td>0</td>
<td>497</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>Protein, mg/dL</td>
<td>31</td>
<td>65</td>
</tr>
<tr>
<td>History of seizure before or at the time of presentation</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bacterial pathogen isolated (both from cerebrospinal fluid and urine)</td>
<td><em>Escherichia coli</em></td>
<td><em>Escherichia coli</em></td>
</tr>
</tbody>
</table>

SI conversion: To convert glucose to mmol/L, multiply by 0.0555.

**COMMENT**

We have previously derived and validated the Bacterial Meningitis Score at a single institution to identify children with CSF pleocytosis who are at very low risk of bacterial meningitis. In the current multicenter validation study in the era of widespread pneumococcal conjugate vaccination, the Bacterial Meningitis Score accurately identified patients at very low risk of bacterial meningitis, misclassifying only 0.1% of patients categorized as very low risk for bacterial meningitis. Our attempts to refine the model using recursive partitioning analysis led us to a somewhat simpler model that relied on CSF-blood glucose ratio less applicable. Furthermore, a prediction rule using a complicated fractional polynomial equation to calculate risk of bac-

©2007 American Medical Association. All rights reserved.
terial meningitis would require automation to be applied in the clinical setting.10,32 Previously published prediction rules were derived before the introduction of conjugate H influenzae type b28 and S pneumoniae vaccines,1,20–35 and were not internally validated or externally validated.12,28–35 In contrast, the Bacterial Meningitis Score provides a simple scoring system composed of easily collected data elements that could routinely be implemented by clinicians in the acute management of children with CSF pleocytosis. To our knowledge, this is the first bacterial meningitis prediction model to be both studied in the era of widespread conjugate pneumococcal vaccine use and externally validated.

Our validation study was conducted using strict methodological standards.13,18,30 Our inclusion and exclusion criteria were such that only those patients with CSF pleocytosis who could be reasonably considered for outpatient management were included in the study (ie, we excluded patients with other reasons for hospital admission or with critical illness). Both the predictors and outcome measure were clearly and objectively defined. By careful standardized chart reviews, we had minimal missing data for the included clinical and laboratory predictors and were able to assign an appropriate outcome (aseptic vs bacterial meningitis) for all patients.

The Bacterial Meningitis Score has already been independently validated (prospectively and retrospectively) in 2 small pediatric studies in France and Belgium (166 and 277 study patients with meningitis, respectively), and shown to perform very well.37,38 None of the patients classified by the Bacterial Meningitis Score in the very low risk category had bacterial meningitis (negative predictive value, 100% for both studies). Although a large prospective validation would be preferable to a retrospective validation, such a study would be difficult to accomplish given the very low incidence of bacterial meningitis. Four of the 5 predictors in the Bacterial Meningitis Score are objective laboratory measures and the fifth, a history of seizure, is a fairly objective clinical measure. Patients were classified as having a seizure for any abnormal neurological activity thought to possibly be a seizure to minimize the risk of variability in interpretation. Therefore, we think our study is nearly equivalent to a prospective validation. Thus, based on the 2 small studies and our validation study, our findings are likely to be widely generalizable and helpful in guiding clinical decision making, as the patient population encompasses a wide spectrum of ages, clinical settings, geographic regions, and seasons.

Our study has some limitations. First, our study was retrospective and therefore subject to potential information bias. However, the potential impact of this limitation is minimal because the Bacterial Meningitis Score includes only objective clinical characteristics and laboratory parameters. Furthermore, we used strict criteria to define the outcome variable (bacterial meningitis) to minimize misclassification bias. Cerebrospinal fluid cultures were available for all included patients and blood cultures were available for 90% of the study patients. Although it is conceivable that some of the patients with no blood culture obtained may have had bacterial meningitis, this seems unlikely given that CSF cultures were negative in all of these patients. In addition, none of the patients who did not have blood cultures drawn (except for those with Lyme meningitis) received a standard course of antibiotics for bacterial meningitis or a diagnosis of bacterial meningitis by the treating clinician. It is also possible that we may have missed potentially eligible study patients due to errors in emergency department diagnosis coding. However, we attempted to capture all cases of children with bacterial meningitis by cross-checking the institution’s microbiology test results and by including all patients with CSF cultures growing bacterial pathogens.

Because our model was designed to identify patients at very low risk for bacterial meningitis, some patients with no predictors of bacterial meningitis may nevertheless have infections that require antimicrobial therapy, such as Lyme meningitis or herpes simplex virus encephalitis. Therefore, the Bacterial Meningitis Score should be used in concert with careful clinical assessment of the patient, which would include consideration of these other important treatable infections. In addition, the Bacterial Meningitis Score is designed to serve as an assistive clinical prediction rule to help guide clinical decision making, and not to serve as a directive decision rule that explicitly dictates clinical care.13 We would particularly caution against the use of the Bacterial Meningitis Score for infants younger than 2 months for whom the Bacterial Meningitis Score may be less accurate, and who may not be appropriate candidates for outpatient management. In this subgroup of the 792 children younger than 2 months (of whom 26 had bacterial meningitis), the classification performance of the Bacterial Meningitis Score was sensitivity of 92.3% (95% CI, 74.9%-99.1%), specificity of 56.3% (95% CI, 52.7%-59.8%), and negative predictive value of 99.5% (95% CI, 98.3%-99.9%). Finally, the Bacterial Meningitis Score should also not be used to guide decision making for children pretreated with antibiotics in whom the diagnosis of aseptic meningitis is difficult and whose pretreatment may have affected CSF profiles.22,23

For patients with at least 1 Bacterial Meningitis Score risk factor or who are younger than 2 months, we suggest admission to the hospital and administration of parenteral antibiotics. For the 2111 patients older than 2 months in our study (of whom 95 had bacterial meningitis), the Bacterial Meningitis Score was highly accurate. The classification performance of the Bacterial Meningitis Score for identifying bacterial meningitis for these children was sensitivity of 100% (95% CI, 96.9%-100%), specificity of 63.5% (95% CI, 61.4%-65.6%), and negative predictive value of 100% (95% CI, 99.8%-100%). For patients older than 2 months with a Bacterial Meningitis
Score of 0 and who are well appearing, physicians could consider 2 options: admission for observation or, in the proper clinical context and if adequate follow-up is available, outpatient management. Because the consequences of missing bacterial meningitis could be devastating, however, we would recommend serious consideration of administration of a long-acting parenteral antibiotic if the patient is to be discharged from the emergency department.

In the conjugate H influenzae type b and pneumococcal vaccines era, bacterial meningitis has become an uncommon disease in US children. Therefore, the majority of children with CSF pleocytosis have aseptic rather than bacterial meningitis. Furthermore, our study confirms that most children with CSF pleocytosis are admitted to the hospital to receive parenteral antibiotics while awaiting bacterial culture test results. Using the Bacterial Meningitis Score prediction rule to assist with clinical decision making could substantially reduce unnecessary hospital admissions for children with CSF pleocytosis at very low risk of bacterial meningitis. Future investigations should study the clinical implementation of the Bacterial Meningitis Score as a guide to help care for children with CSF pleocytosis.

Author Affiliations: Department of Medicine, Children’s Hospital Boston and Harvard Medical School, Boston, Mass (Dr Nigrovic and Malley); Departments of Emergency Medicine (Dr Kuppermann) and Pediatrics (Drs Nigrovic and Truong), University of Colorado School of Medicine, Denver; Department of Pediatrics, Texas Children’s Hospital and Baylor College of Medicine, Houston (Dr Malley); Department of Emergency Medicine, Rady Children’s Hospital San Diego Medical Center (Dr Kanegaye) and Department of Pediatrics, University of California, San Diego School of Medicine, San Diego; Department of Pediatrics, Children’s Mercy Hospitals and Clinics and University of Missouri-Kansas City School of Medicine, Kansas City (Dr Schremmer); Department of Pediatrics, Children’s Hospital of Philadelphia and University of Pennsylvania, Philadelphia (Dr Schweb); Department of Emergency Medicine, Children’s National Medical Center and George Washington University School of Medicine, Washington, DC (Dr Agrawal); Department of Emergency Medicine, Children’s Hospital and Research Center Oakland, Oakland, Calif (Dr Mansour); Department of Pediatrics, Alfred I. duPont Hospital for Children and Thomas Jefferson Medical College, Wilmington, Del (Dr Bennett); Department of Pediatrics, Children’s Memorial Hospital and Northwestern University Feinberg School of Medicine, Chicago, Ill (Dr Katsogridakis); Department of Emergency Medicine, Children’s Medical Center, Atlanta, Ga (Dr Bandopadhyay); Department of Emergency Medicine, Phoenix Children’s Hospital and University of Arizona College of Medicine, Phoenix (Dr Bulloch); Departments of Emergency Medicine and Pediatrics, Hadassah Medical Center and Brown Medical School, Providence, RI (Dr Steele); Department of Emergency Medicine, Children’s Hospital and Regional Medical Center, and University of Washington School of Medicine, Seattle (Dr Kaplan); Department of Pediatrics, Le Bonheur Children’s Medical Center and University of Tennessee Health Science Center, College of Medicine, Memphis (Dr Herman); Department of Emergency Medicine, Children’s Hospital of Wisconsin and Medical College of Wisconsin, Milwaukee, and Pediatric Medicine Associates LLC, Children’s HealthCare of Atlanta at Scottish Rite, Atlanta, Ga (Dr Bandopadhyay), Department of Emergency Medicine, Morgan Stanley Children’s Hospital of New York-Presbyterian and Columbia University College of Physicians and Surgeons, New York, NY (Dr Dayan); Department of Pediatrics, Children’s Hospital Los Angeles and Keck School of Medicine, University of Southern California, Los Angeles (Dr Wang); and Department of Emergency Medicine, Children’s Hospital, The Ohio State University, Columbus (Dr Bonsu and Chapman).

Author Contributions: Dr Nigrovic had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Nigrovic, Kuppermann, Malley.

Acquisition of data: Nigrovic, Macias, Cannavino, Moro-Sutherland, Schremmer, Schwab, Agrawal, Mansour, Bennett, Katsogridakis, Mohseni, Bulloch, Steele, Kaplan, Herman, Bandopadhyay, Dayan, Truong, Wang, Bonsu, Chapman, Kanegaye.

Analysis and interpretation of data: Nigrovic, Kuppermann, Malley.

Drafting of the manuscript: Nigrovic, Kuppermann, Malley.

Critical revision of the manuscript for important intellectual content: Macias, Cannavino, Moro-Sutherland, Schremmer, Schwab, Agrawal, Mansour, Bennett, Katsogridakis, Mohseni, Bulloch, Kaplan, Herman, Bandopadhyay, Dayan, Truong, Wang, Bonsu, Chapman, Kanegaye.

Statistical analysis: Nigrovic, Kuppermann, Malley.

Obtained funding: Nigrovic, Kuppermann, Malley.

Financial Disclosures: None reported.

Members of the Pediatric Emergency Medicine Collaboration Research Committee of the American Academy of Pediatrics Scientific Review Committee are Denise Dowd, MD, Children’s Mercy Hospitals and Clinics and University of Missouri-Kansas City School of Medicine, Kansas City; Marc Gorelick, MD, Children’s Hospital of Wisconsin and Medical College of Wisconsin, Milwaukee; Louis C. Hamper, MD, MBA, University of Colorado School of Medicine and The Children’s Hospital, Denver; Philip Scibano, MD, Columbus Children’s Hospital and The Ohio State University College of Medicine, Columbus; and Milton K. Tenenbein, MD, Children’s Hospital Winnipeg and University of Manitoba, Winnipeg.

Funding/Support: This work was supported by the Ambulatory Pediatric Association Young Investigator Grant and the National Research Service Award (T32 HD40128-01; Research Training in Pediatric Emergency Medicine), which was awarded to Dr Nigrovic.

Role of the Sponsor: The sponsor did not participate in the design or conduct of the study, in the collection, management, analysis, or interpretation of the data, or in the preparation, review, or approval of the manuscript. All members of the Scientific Review Committee of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics reviewed the study protocol.

Acknowledgment: We thank other members of the study group, including those who helped with chart abstraction, data entry, and database management: Elizabeth R. Alpern, MD, MSCE (Children’s Hospital of Philadelphia and University of Pennsylvania, Philadelphia); Troy Bush (Texas Children’s Hospital and Baylor College of Medicine, Houston), Joseph M. Campos, PhD (Children’s National Medical Center, Washington, DC), Murray Edelberg, PhD (Carlisle, Mass), Kim Fisher, PhD (Center for Pediatric Research, University of Tennessee, Memphis), Marissa Hauptman (Brown Medical School, Providence, RI), Paul Ishimine, MD (Rady Children’s Hospital San Diego Medical Center and University of California, San Diego School of Medicine, San Diego), Daniel M. Kaplan (Children’s National Medical Center and George Washington University School of Medicine, Washington, DC), John Leake, MD, and R. Ian McCaslin, MD, MPH (Rady Children’s Hospital San Diego Medical Center and University of California, San Diego School of Medicine, San Diego), Limair Salim (Center for Pediatric Research, University of Tennessee, Memphis), James Wilde, MD (Children’s Medical Center and Medical College of Georgia, Augusta), and Xiao Zhao (Brookline, Mass).None of the persons acknowledged received any financial compensation for their work.

REFERENCES


©2007 American Medical Association. All rights reserved.
validation of a clinical prediction rule for bacterial meningitis